IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 7608
Erion *et al.*	Art Unit: 1624
Appl. No.: 09/518,501	Examiner: T. McKenzie
Filed: March 3, 2000	Atty. Docket: 2358.0010002/RWE/CJW
For: **Novel Phosphorus-containing Prodrugs**	

Supplemental Information Disclosure Statement

Mail Stop RCE

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Listed on accompanying IDS Forms are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. Copies of documents B1-B3 and C1-114 are submitted. However, in accordance with 37 C.F.R. § 1.98(a)(2), no copies of U.S. patents and patent application publications cited on the attached IDS Forms are submitted.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This Supplemental Information Disclosure Statement is being filed concurrently with a Request for Continued Examination. No fee or statement is required.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Attorney for Applicants
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Date: December 20, 2005

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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Sheet 1 of 12

Application No.	09/518,501
Filing Date	03/03/2000
First Named Inventor	Mark D. Erion
Art Unit	1624
Examiner Name	Thomas C. McKenzie
Attorney Docket No.	2358.0010002 (MTI-013.US)

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant	Relevant Pages
	A1	3,796,700	03/12/1974	Yoshioka et al.	all
	A2	4,255,566	03/10/1981	Carrico et al.	all
	A3	4,318,982	03/09/1982	Hornby et al.	all
	A4	4,340,668	07/20/1982	Hornby et al.	all
	A5	4,376,165	03/08/1983	Hornby et al.	all
	A6	4,447,529	05/08/1984	Greenquist et al.	all
	A7	4,804,655	02/14/1989	Müller et al.	all
	A8	5,204,355	04/20/1993	Zsadon et al.	all
	A9	5,212,304	05/18/1993	Fung et al.	all
	A10	5,258,538	11/02/1993	Fung et al.	all
	A11	6,117,873	09/12/2000	Acklin et al.	all
	A12	6,752,981 B1	06/22/2004	Erion et al.	all
	A13	6,756,360 B1	06/29/2004	Erion et al.	all

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document (Cty code-number-kind)	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant	Relevant Pages	T[1]
	B1	WO 91/19721 A1	12/26/1991	Glazier, Arnold	all	
	B2	WO 97/22614 A1	06/26/1997	Chiroscience Ltd.	all	
	B3	WO 01/39724 A2	06/07/2001	Regents of Univ. of Calif.	all	
					all	

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Description	T[1]
	C1	ALARCON, R.A., "Studies on the In Vivo Formation of Acrolein: 3-Hydroxy-propylmercapturic Acid as an Index of Cyclophosphamide (NSC-26271) Activation," *Cancer Treatment Reports* 60(4), 327-335, U.S. National Cancer Institute (1976).	
	C2	ALEXANDER, P. et al., "Preparation of 9-(2-Phosphonomethoxyethyl) Adenine Esters as Potential Prodrugs," *Collect. Czech. Chem. Commun.* 59, 1853-1869, Nakladatelstvi Ceskoslovenski Akademie Ved. (1994).	
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	C9	BALTHAZOR, T.M. et al., "Nickel-Catalyzed Arbuzov Reaction: Mechanistic Observations," *J. Org. Chem.* 45, 5425-5426, American Chemical Society (1980).	
	C10	BEDFORD, S.B. et al., "Synthesis of Water-Soluble Prodrugs of the Cytotoxic Agent Combretastatin A4," *Bioorg. Med. Chem. Lett.* 6(2), 157-160, Elsevier Science Ltd. (1996).	

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	Art Unit	1624
	Examiner Name	Thomas C. McKenzie
	Attorney Docket No.	2358.0010002 (MTI-013.US)

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Description	T[1]
	C11	Beilstein Registry Number 3635189, *Beilstein Institut zur Foerderung der Chemischen Wissenschaften* (1991).	
	C12	BENTRUDE, W.G. et al., "Stereo- and Regiochemistries of the Oxidations of 2-Methoxy-5-*tert*-butyl-1,3,2-dioxaphosphorinanes and the Cyclic Methyl 3'5'-Phosphite of Thymidine by H_2O/I_2 and O_2/AIBN to P-Chiral Phosphates. ^{17}O NMR Assignment of Phosphorus Configuration to the Diasteromeric Thymidine Cyclic Methyl 3'5'-Monophosphates," *J. Am. Chem. Soc.* 111, 3981-3987, American Chemical Society (1989).	
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	C18	BORCH, R.F. et al., "Synthesis, Activation and Cytotoxicity of Aldophosphamide Analogues," *J. Med. Chem.* 34, 3052-3058, American Chemical Society (1991).	
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	Art Unit	1624
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	Attorney Docket No.	2358.0010002 (MTI-013.US)

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Description	T[1]
	C22	BRENNA, O. et al., "Affinity-Chromatography Purification of Alkaline Phosphatase from Calf Intestine," *Biochem. J.* 151, 291-296, Portland Press on behalf of The Biochemical Society (1975).	
	C23	BRILL, T.B. et al., "Arbuzov-like Dealkylation Reactions of Transition-Metal-Phosphite Complexes," *Chem. Rev.* 84, 577-585, American Chemical Society (1984).	
	C24	BROCK, N. et al., "Acrolein, the Causative Factor of Urotoxic Side-effects of Cyclophosphamide, Ifosfamide, Trofosfamide and Sufosfamide" *Arzneimittel Forschung Drug Research* 29(4), 659-661, Editio Cantor (1979).	
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	C26	CAMPBELL, D.A., "The Synthesis of Phosphonate Esters, an Extension of the Mitsunobu Reaction," *J. Org. Chem.* 57, 6331-6335, American Chemical Society (1992).	
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	C31	CHEN, L. et al., "Sensitization of Human Breast Cancer Cells to Cyclophosphamide and Ifosfamide by Transfer of a Liver Cytochrome P450 Gene," *Cancer Research* 56, 1331-1340, American Association for Cancer Research (1996).	
	C32	CLARK, L. et al., "Oxidative Metabolism of Cyclophosphamide: Identification of the Hepatic Monooxygenase Catalysts of Drug Activation," *Cancer Research* 49, 2344-2350 American Association for Cancer Research (1989).	

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	Attorney Docket No.	2358.0010002 (MTI-013.US)

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Description	T[1]
	C33	DAVIS, L. et al., "Effect of *Withania somnifera* on Cyclosphosphamide-induced Urotoxicity," *Cancer Letters* 148, 9-17, Elsevier Science Ireland Ltd. (January 2000).	
	C34	DEARFIELD, K.L. et al., "Analysis of the Genotoxicity of Nine Acrylate/Methacrylate Compounds in L5178Y Mouse Lymphoma Cells," *Mutagenesis* 4, 381-393, IRL Press, Oxford (1989).	
	C35	DELEVE, L.D. et al., "Cellular Target of Cyclophosphamide Toxicity in the Murine Liver: Role of Glutathione and Site of Metabolic Activation," *Hepatology* 24(4), 830-837, American Association for the Study of Liver Diseases (1996).	
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	C38	DICKSON, J.K. et al., "Orally Active Squalene Synthase Inhibitors: Bis((acyloxy)alkyl) Prodrugs of the α-Phosphonosulfonic Acid Moiety," *J. Med. Chem.* 39, 661-664, American Chemical Society (1996).	
	C39	ENRIQUEZ, P.M. et al., "Conjugation of Adenine Arabinoside 5'-Monophosphate to Arabinogalactan: Synthesis, Characterization, and Antiviral Activity," *Bioconjugate Chem.* 6, 195-202, American Chemical Society (1995).	
	C40	ERION, M.D. et al., "Design, Synthesis, and Characterization of a Series of Cytochrome P_{450} 3A-Activated Prodrugs (HepDirect Prodrugs) Useful for Targeting Phosph(on)ate-Based Drugs to the Liver," *J. Am. Chem. Soc.* 126, 5154-5163, American Chemical Society (April 2004).	
	C41	ERION, M.D. et al., "Liver-Targeted Drug Delivery Using HepDirect Prodrugs," *J. of Pharmacology & Experimental Therapeutics* 312(2), 554-560, The American Society for Pharmacology and Experimental Therapeutics (February 2005).	
	C42	FARQUHAR, D. et al., "Biologically-Cleavable Phosphate Protective Groups: 4-Acyloxy-1,3,2-Dioxaphosphorinanes as Neutral Latent Precursors of Dianionic Phosphates," *Tetrahedron Lett.* 36(5), 655-658, Elsevier Science Ltd. (1995).	

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	Attorney Docket No.	2358.0010002 (MTI-013.US)

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Description	T[1]
	C43	FIUME, L. et al., "Inhibition of Hepatitis B Virus Replication by Vidarbine Monophosphate Conjugated with Lactosaminated Serum Albumin," *The Lancet* 13-15, Lancet Publishing Group (1988).	
	C44	FRAISER, L. et al., "Murine Strain Differences in Metabolism and Bladder Toxicity of Cyclophosphamide," *Toxicology* 75, 257-272, Elsevier Scientific Publishers (1992).	
	C45	GAO, Y. et al., "Asymmetric Synthesis of Both Enantiomers of Tomoxetine and Fluoxetine. Selective Reduction of 2,3-Epoxycinnamyl Alcohol with Red-A1," *J. Org. Chem.* 53, 4081-4084, American Chemical Society (1988).	
	C46	GILARD, V. et al., "Chemical Stability and Fate of the Cytostatic Drug Ifosfamide and Its N-Dechloroethylated Metabolities in Acidic Aqueous Solutions," *J. Med. Chem.* 42, 2542-2560, American Chemical Society (July 1999).	
	C47	GROEN, A.K. et al., "Intracellular Compartmentation and Control of Alanine Metabolism in Rat Liver Parenchymal Cells," *Eur. J. Biochem.* 122, 87-93, FEBS (1982).	
	C48	GUIDA, W.C. et al., "Structure-Based Design of Inhibitors of Purine Nucleoside Phosphorylase. 4. A Study of Phosphate Mimics," *J. Med. Chem.* 37, 1109-1114, American Chemical Society (1994).	
	C49	GURTOO, H.L. et al., "Role of Glutathione in the Metabolism-dependent Toxicity and Chemotherapy of Cyclophosphamide," *Cancer Research* 41, 3584-3591, American Association for Cancer Research (1981).	
	C50	GUSTIN, N.C. et al., "A Rapid, Sensitive Assay for Adenosine Deaminase," *Analytical Biochemistry* 71, 527-532, Academic Press, Inc. (1976).	
	C51	HAYAKAWA, Y. et al., "Benzimidazolium Triflate as an Efficient Promoter for Nucleotide Synthesis via the Phosphoramidite Method," *J. Org. Chem.* 61, 7996-7997, American Chemical Society (1996).	
	C52	HILTON, J., "Role of Aldehyde Dehydrogenase in Cyclophosphamide-resistant L1210 Leukemia," *Cancer Research* 44, 5156-5160, American Association for Cancer Research (1984).	
	C53	HIRAYAMA, N. et al., "Structure and Conformation of a Novel Inhibitor of Angiotensin I Converting Enzyme - a Tripeptide Containing Phosphonic Acid," *Int. J. Pept. Protein Res.* 38, 20-24, Munksgaard International Publishers (1991).	

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	C54	JOUNAIDI, Y. et al., "Frequent, Moderate-Dose Cyclophosphamide Administration Improves the Efficacy of Cytochrome P-450/Cytochrome P-450 Reductase-based Cancer Gene Therapy," *Cancer Research* 61, 4437-4444, American Association for Cancer Research (June 2001).	
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	C57	KELLEY, J.L. et al., "[[(Guaninylalkyl)phosphinico] methyl] phosphonic Acids. Multisubstrate Analogue Inhibitors of Human Erythrocyte Purine Nucleoside Phosphorylase," *J. Med. Chem.* 38, 1005-1014, American Chemical Society (1995).	
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	C60	KWON, C.-H. et al., "Effects of N-Substitution on the Activation Mechanisms of 4-Hydroxycyclophosphamide Analogues," *J. Med. Chem.* 32, 1491-1496, American Chemical Society (1989).	
	C61	LILO, B. et al., "Synthesis and Configurational Assignment of Bicyclic 'Preactivated' Analogues of Cyclophosphamide," *Tetrahedron Letters* 31(6), 887-890, Pergamon Press plc. (1990).	
	C62	LOW, J.E. et al., "Conversion of 4-Hydroperoxycyclophosphamide and 4-Hydroxycyclophosphamide to Phosphoramide Mustard and Acrolein Mediated by Bifunctional Catalysts," *Cancer Research* 42, 830-837, American Association for Cancer Research (1982).	
	C63	LU, X. et al., "Palladium-Catalyzed Reaction of Aryl Polyfluoroalkanesulfonates with *O,O*-Dialkyl Phosphonates," *Synthesis* 726-727, Academic Press (1987).	
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	C65	LUDEMAN, S.M. et al., "Synthesis and Antitumor Activity of Cyclophosphamide Analogues. 2. Preparation, Hydrolytic Studies, and Anticancer Screening of 5-Bromocyclophosphamide, 3,5-Dehydrocyclophosphamide, and Related Systems," *J. Med. Chem.* 22(2), 151-158, American Chemical Society (1979).	
	C66	LUDEMAN, S.M. et al., "Synthesis of Reactive Metabolite-Analogues of Cyclophosphamide for Comparisons of NMR Kinetic Parameters and Anticancer Screening Data," *Drugs Exptl. Clin. Res.* XII 6/7, 527-532, Bioscience Ediprint Inc. (1986).	
	C67	MAY-MANKE, A. et al., "Investigation of the Major Human Hepatic Cytochrome P450 Involved in 4-Hydroxylation and N-dechloroethylation of Trofosfamide," *Cancer Chemother. Pharmacol.* 44, 327-334, Springer-Verlag (August 1999).	
	C68	MAYNARD-FAURE, P. et al., "New Strategy for the Diastereoselective Synthesis of Bicyclic 'Pre-activated' Analogues of Cyclophosphamide," *Tetrahedron Letters* 39, 2315-2318, Elsevier Science Ltd. (April 1998).	
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	C73	MELVIN, L.S., "An Efficient Synthesis of 2-Hydroxyphenylphosphonates," *Tetrahedron Lett.* 22(35), 3375-3376, Pergamon Press Ltd. (1981).	
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	Filing Date	03/03/2000
	First Named Inventor	Mark D. Erion
	Art Unit	1624
	Examiner Name	Thomas C. McKenzie
	Attorney Docket No.	2358.0010002 (MTI-013.US)

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Examiner Initials*	Cite No.	Description	T[1]
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	C87	PITCHER, H.R., "Built-in Bypass," *Nature* 429, 39, Nature Publishing Group (May 2004).	
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	C89	REDDY, M.R. et al., "Development of a Quantum Mechanics-Based Free-Energy Perturbation Method: Use in the Calculation of Relative Solvation Free Energies," *J. Am. Chem. Soc.* 126, 6224-6225, American Chemical Society (May 2004).	
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	C112	YIP, K.F. et al., "Use of High-Performance Liquid Chromatography in the Preparation of Flavin Adenine Dinucleotide Analyte Conjugates," *J. of Chromatography* 326, 301-310, Elsevier Science Publishers B.V., Amsterdam (1985).	
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